UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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ORTHOPEDIC AND REHABILITATION DEVICES PANEL

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THURSDAY, SEPTEMBER 8, 2005

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The meeting was held in Salons A, B, and C of the Hilton Washington, D.C. North, 620 Perry Parkway, Gaithersburg, Maryland, at 8:34 a.m., Dr. Sanjiv H. Naidu, Acting Panel Chairperson, presiding.

PRESENT:
SANJIV H. NAIDU, M.D. Ph.D., ACTING PANEL CHAIR

BRENT A. BLUMENSTEIN, Ph.D., DEPUTIZED VOTING MEMBER

CHOLL W. KIM, M.D., Ph.D., VOTING MEMBER

JAY D. MABREY, M.D., DEPUTIZED VOTING MEMBER

MICHAEL B. MAYOR, M.D., DEPUTIZED VOTING MEMBER

HARRY B. SKINNER, M.D., Ph.D., DEPUTIZED VOTING MEMBER

PAMELA ADAMS, INDUSTRY REPRESENTATIVE

PRESENT (Continued):

CONNIE F. WHITTINGTON, MSN, RN, CONSUMER REPRESENTATIVE

JANET L. SCUDIERO, M.S., EXECUTIVE SECRETARY

MARK MELKERSON, M.S., FDA

C O N T E N T S

P R O C E E D I N G S

(8:34 a.m.)

MS. SCUDIERO: Good morning. We're ready to being this meeting of the Orthopedic and Rehabilitation Devices Panel.

I am Jan Scudiero, the Executive Secretary of this panel and a reviewer in the Division of General Restorative and Neurological Devices.

First, the usual housekeeping matters. If you haven't already done so, please sign the attendance sheets that are on the tables by the door.

Information on today's agenda and for panel meeting minutes and transcripts as well is there.

The next tentatively scheduled meeting for this panel on November 3rd and 4th is canceled because there's no agenda item ready for panel review.

Upcoming panel meetings are announced on an Advisory Panel Web site, the Federal Register and in the telephone information line. Please monitor the Web site for future meeting announcements.

Finally, as a courtesy to others in the

room, please, turn off or put on silence your cell phones during the meeting.

Thank you.

Dr. John Kirkpatrick is unable to be with us today.

I will now read into the record three agency statements prepared for this meeting. They are the appointment of temporary panel chair statement, the appointment of temporary voting member statement, and the conflict of interest statement.

First, I appoint Sanjiv H. Naidu, M.D., Ph.D., a voting member of the Orthopedic and Rehabilitation Devices Panel as Acting Panel Chair for the September 8th and 9th, 2005 meeting of the panel, and this was signed by Dr. Daniel G. Schultz, Director, Center for Devices and Radiological Health, on September 7th.

The appointment to temporary voting status: pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27th, 1990, and amended April 20th, 1995, I appoint the following as voting members of the

Orthopedic and Rehabilitation Devices Panel for the duration of this meeting on September 8th, 2005: Brent A. Blumenstein, Ph.D., Jay D. Mabrey, M.D., Michael B. Mayor, M.D., and Harry B. Skinner, M.D. Ph.D.

For the record, these people are special government employees and are consultants to this panel or another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

The conflict of interest statement: the Food and Drug Administration is convening today's meeting of the Orthopedic and Rehabilitation Device Panel of the Medical Devices Advisory Committee, under the authority of the Federal Advisory Committee Act, FACA, of 1972.

The panel meetings provide transparency into the agency's deliberative processes. With the exception of the industry rep. all members of the committee are special government employees, or SGEs, or regular federal employees from other agencies and

are subject to federal conflict of interest laws and regulations.

Consequently, in the interest of transparency and in the spirit of disclosure, the following information on the status of this panel's compliance with federal ethics and conflict of interest laws as covered by, but not limited to those found at Part 18, U.S. Code 208, and Part 21, U.S. Code, Section 355(n)(4). This is being provided to the participants in today's meeting and to the public.

FDA has determined that the members of this panel are in compliance with the federal ethics and conflict of interest laws, including, but not limited to, Part 18 U.S. Code Section 208, and Part 21, U.S. Code Section 355(n)(4). Under Part 18 U.S. Code Section 208, applicable to all government agencies and Part 21 U.S. Code Section 355(n)(4), applicable to FDA, Congress has authorized FDA to grant waivers to special government employees who have limited financial conflict when it is determined that the agencies need for the particular individual's services outweighs his or her potential financial

conflict of interest.

Members who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse, or minor child, related to the discussions of today's meeting. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching or speaking and writing, patents and royalties, and primary employment.

Today's agenda involves the review of a pre-market approval application, PMA, for a hip resurfacing system in tended to relieve hip pain and improve hip function in patients who have adequate bone stock and are at risk of requiring more than one hip joint replacement over their lifetimes.

This is a particular matters meeting during which specific matters related to the PMA will be discussed.

In accordance with Part 18, U.S. Code Section 208(b)(3), a full waiver has been granted to Dr. Michael Mayor. Dr. Mayor's waiver involves a patent licensed to assist a company of a competitor. He receives less than $15,001 in royalties for the patent.

Copies of each acknowledgement and consent to disclosure statement signed by each participant at today's meeting who received a conflict of interest waiver along with the statement will be available for review at the registration table during the meeting and will be includes as part of official meeting transcript.

A copy of the written conflict of interest statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn building.

Lastly, Ms. Pamela Adams is the industry rep. acting on behalf of all related industry and is employed by Etex Corporation, Incorporated. In the event that the discussions involves any other products or firms not already on the agenda for which an FDA

participant may have a financial interest, all meeting participants are reminded that they're required by Part 18, U.S. Code 208, to exclude themselves from such deliberations and announce their exclusion for the record.

Finally, in the interest of public transparency with respect to all other participants, we ask that they publicly disclose prior to making any statements any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

I would now like to turn the meeting over to Dr. Naidu, our Acting Chairman for the day.

PANEL CHAIRPERSON NAIDU: Good morning. My name is Sanjiv Naidu. I am the Acting Chairperson for the Orthopedic and Rehabilitation Devices Panel today. I'm Professor of Orthopedic Surgery at Penn State College of Medicine, and I'm also a materials scientist.

At this meeting the panel will be making a recommendation to the FDA on the approvability of the

pre-market application, P040033, for the Smith & Nephew Birmingham resurfacing hip system, the BHR system. It is a hip joint, metal on metal, semi-constrained, hybrid prosthesis, cemented femoral component, uncemented acetabular component. It is intended to relieve hip pain and improve hip function in patients who have adequate bone stock and are at risk of requiring more than one hip joint replacement over their lifetimes.

Before we begin, I would like to ask our distinguished panel members who are generously giving their time to help FDA in the matter being discussed today and the other FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

Mr. Melkerson, if you could start off.

MR. MELKERSON: I'm Mark Melkerson. I'm the Acting Director for the Division of General Restorative and Neurological Devices.

DR. MAYOR: Michael Mayor, orthopedic surgeon, Professor of Orthopedics at the Dartmouth-Hitchcock Medical Center and the Dartmouth Medical

School. I'm co-director of the Thayer Engineering School, Dartmouth Biomedical Engineering Laboratories.

DR. BLUMENSTEIN: Brent Blumenstein, a biostatistician working out of Seattle.

DR. MABREY: Jay Mabrey, orthopedic surgeon, Medical Director of the Orthopedic Motion and Sports Performance Laboratory at Baylor University Medical Center and also Chief of Orthopedics at Baylor University Medical Center in Dallas.

DR. KIM: I'm Choll Kim. I'm the Assistant Professor of Orthopedic Surgery at the University of California, San Diego. I'm the Director of the Spine Research Lab there.

DR. SKINNER: My name is Harry Skinner. I'm Professor and Chair of Orthopedic Surgery at the University of California, Irvine.

MS. WHITTINGTON: My name is Connie Whittington. I'm an orthopedic clinical nurse specialist at Piedmont Hospital where I serve as the Coordinator for Orthopedic Research.

MS. ADAMS: I'm Pamela Adams. I'm Chief Operating Officer at Etex Corporation.

PANEL CHAIRPERSON NAIDU: Thank you.

I would like to note that for the record that the voting members present constitute a quorum as required by 21 CFR Part 14.

There will be two brief presentations before the main agenda topic. First is Dr. Susan Gardner who will speak on post market study design.

DR. GARDNER: Okay. Good morning. I'm going to spend just a few minutes telling you about an important programmatic change that has taken place in the center.

The essence of the change is a move of the condition of approval studies program from the Office of Device Evaluation to the Office of Surveillance and Biometrics.

Briefly, the Office of Surveillance and Biometrics is involved both in premarket and post market activities. We're involved in the premarket review because the statisticians and the epidemiologists of the center are in the Office of Surveillance and Biometrics, and we also have a major role in the post market in that all the adverse events

and the post market monitoring tools, the medical device reporting system, and the MedSun program are in OSB.

We're also responsible for analyzing the data to come in on these post market monitoring tools and characterizing the risk and working with the rest of the center to identify post market problems and take action on those. We're responsible for coordinating the center response to health care professionals in risk communication, and we're responsible for interpretation of the medical device reporting regulation.

The legislative 21 CFR 814.82 says that post approval requirements can include continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use, and this is the basis of the condition of approval studies program.

The impetus for the change came from a study, an internal evaluation that we did in CDRH of our CoA Program. We look at this in about 2000, 2001, and we went back and we looked at all of the PMAs that

had been approved from 1998 through the year 2000. There were 127 PMAs, and 45 of those had condition of approval orders.

And what we found unfortunately is that we were really unable to find some of these studies, and we realized this was because we had no standardized tracking procedures for tracking the results of these studies. As one might expect there had been a turnover in lead reviewers as people naturally moved through the organization or changed jobs, and also that in ODE with their focus on premarket, it was really difficult for them under their current resources to continue to follow these studies and give them the attention that they need.

So we came up with a plan to change the program. The point of the change or the goal of the change was to make sure that we could obtain this post market information at this critical period when the device enters the market and we could continue to assess the safety and effectiveness as the device moves from the clinical trial into the real world use, and this obviously would allow us to better

characterize the risk-benefit profile and add to our ability to make sound scientific decisions as we continue to monitor these devices.

We actually did a pilot that went for about two years. So when we officially changed the program on January 1st of 2005, we were fairly well prepared, and in addition to that a number of studies already were being monitored in OSB. We have developed and instituted an automatic tracking system that is up and working, and not only do we have studies being tracked from January 2005. We've gone back to pick up studies that have been approved earlier. So we're also following those.

The point of the tracking system obviously is to acknowledge to industry when studies are received and to follow up if we don't receive the information that we're supposed to have.

Another fundamental change is we have added an epidemiologist to the PMA review team when we think that we're going to have or it looks likely that we'll have a condition of approval study if the device is approved. The epidemiologist is tasked with the

development of the post market monitoring plan during the premarket review working with the rest of the PMA team. The epidemiologist has the lead for developing, and let me emphasize we're really looking to develop well formulated post market questions and make sure that these studies are important if we're going to ask industry to do them.

The epi person will have the lead in the design of the study protocol and in the evaluation of study progress and results after approval, and so when the results of these studies come into OSB, we will then look at the results and then turn to our colleagues in the premarket arena and go back to the PMA team, review what the progress has been and see if there's anything else that we need to do.

So with these changes, why do we think we will do better? Well, first of all, we think that with a real emphasis on working with industry to make sure that the questions that we're asking in the premarket arena are really important fundamental questions, and we have a good study protocol design. Everybody will be motivated, first of all, to get the

studies done, and secondly, to evaluate them and make sure that the results are important.

For everybody acknowledgement of the work that you do and feedback on the studies motivate people to do it. So, again, industry won't feel that their work is falling into a black hole, and we will be able to interact with them to make sure that the results are on target.

We will be posting the status of the studies on CDRH Web site, and also if studies are not done, we do have the ability under Section 522 to mandate a post market study, but again, we are hoping if people work together to have a good study and a good protocol that we won't have to go there.

What does this mean to the Advisory Panel? Well, first of all, let me emphasize it certainly doesn't change the standards for making sure that the product is reasonably safe and effective before it's approved.

However, during the approval process we will sometimes lay out deliberately and sometimes, of course, it will come up naturally in discussion

questions that deal with the post market piece of the approval process, and your input, your suggestions of possible approaches for the post market pieces or questions that you're concerned about will be really important to us and certainly will be taken under consideration if the device is approved and we decide to do a condition of approval study.

We are also committed to coming back to you; either FDA or industry, to come back to you and give you the results of condition of approval studies after the product is approved.

Any questions?

(No response.)

DR. GARDNER: Thanks.

PANEL CHAIRPERSON NAIDU: Thank you, Dr. Gardner.

Now, Mr. Glenn Stiegman will give us a division update on the activities since 2004 panel meeting.

MR. STIEGMAN: Hi. My name is Glenn Stiegman. This is the panel update for the Orthopedic and Rehabilitation Panel of September 8th and 9th.

Action on items from previous Advisory Committee meetings. From the June 2nd, 2004 meeting, P040006 from the DePuy Spine, the Charite artificial disc. This device was approved October 26th of 2004 for spinal arthroplasty in patients with degenerative disk disease at one level from L4 to S1.

A post approval study to further document the incidence of complications, such as migration and subsidence is ongoing.

Other significant approvals that have occurred since the last panel update, two ceramic on ceramic hips, one on December 17th, 2004, the Smith & Nephew Reflections ceramic acetabular system, which is indicated for patient requiring primary total hip arthroplasty due to noninflammatory arthritis, such as osteoarthritis, avascular necrosis and traumatic arthritis.

On May 4, 2005, the DePuy Orthopedics, the Dura Option ceramic hip system for patients with noninflammatory degenerative joint disease, such as osteoarthritis, avascular necrosis, congenital hip dysplasia, and post traumatic arthritis.

On December 3rd, 2004, P010029, Savient Pharmaceuticals, which has recently been bought out by Ferring Pharmaceuticals, the Nuflexxa one percent sodium hyaluronate for treatment of pain and osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics. This particular device is made by bacterial fermentation instead of being extracted from chicken products like other hyaluronate products.

An HDE, the humanitarian device exemption, H030009 from Synthes USA, the vertical expandable prosthetic titanium rib, which is indicated for the treatment of thoracic insufficiency syndrome. It's going to immature patients. TIS is defined as inability of the thorax to support normal respiration or lung growth.

Other significant 510(k) clearances, February 18th, 2005, Blackstone Medical, we cleared a laminoplasty fixation system for holding bone graft in place during laminoplasty procedures.

From the Zimmer Trabecular Technology, the

trabecular metal osteonecrosis interventional implant which is indicated to treat patients with osteonecrosis of the femoral head.

Guidances that have been published since the last panel update, the clinical data presentations for orthopedic device applications and the clinical trial considerations, vertebral augmentation devices to treat spinal insufficiency fractures.

The Division of General, Restorative, and Neurological Devices staffing changes. The new or permanent orthopedic staff in ORDB, Ronald Jean, Dr. Kristin Mills, John Holden, and Dr. Khan Li have all joined our staff since the last panel update on a permanent or new basis.

Also, no longer with the Orthopedic Devices Branch or FDA, Barbara Zimmerman is now the Deputy Director of the Division of Cardiovascular Devices. Dr. Celia Witten is now the Director of the Office of Cellular Tissue and Gene Therapies at CBER. Dr. Martin Yahiro is moving on to industry on September 17th. Genevieve Hill is returning to school and Dr. Michael Schlosser is returning to private

practice.

Current division staff changes, Mark Melkerson is the Acting Division Director on a four-month detail. Ted Stevens and Barb Buch are both Acting Deputy Division Directors for DGRND. Myself, Glenn Stiegman, is the new Branch Chief of Orthopedic Devices Branch, and Aric Kaiser is currently on a four-month detail on the Office of Surveillance and Biometrics.

And lastly, in conclusion, we'd like to take a moment of silence to remember one of our bright, young, highly esteemed orthopedic device reviewers, Jonathan Lim who passed away last week. More than just a colleague, Jon was a good friend to many and will be sorely missed. Jon's spirit will always live in the pleasant memories that he created in our hearts.

(Pause in proceedings.)

MR. STIEGMAN: Thank you.

PANEL CHAIRPERSON NAIDU: Thank you, Mr. Stiegman.

We will now proceed with the open public

hearing portion of the meeting. Prior to the meeting, two people asked to speak in the open public hearing. They will speak in order of their request to speak.

We ask that you speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of this meeting.

Please state your name and the nature of any financial interest you may have in this or any other medical device company. Ms. Scudiero will now read the open public hearing statement.

MS. SCUDIERO: Both the FDA and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes it is important to understand the context of any individual's presentation.

For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may

have with the sponsor, its products and, if known, its direct competitors.

For example, this information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I would like to note for the record that prior to the meeting three letters with general comments on the agenda item were received. Copies of these letters were given to the panel and the PMA sponsor this morning. These are now part of the record for this meeting.

Dr. Naidu.

PANEL CHAIRPERSON NAIDU: Thank you.

The first open public hearing presented is Dr. Susan Krasny, Vice President of the Orthopedic

Surgical Manufacturers Association.

Dr. Krasny, you have ten minutes.

DR. KRASNY: Thank you.

I am the Senior Director of Regulatory Affairs and Clinical Affairs with Stryker Spine, and I have no financial interest in the sponsor today.

Good morning. My name is Susan Krasny, and I speak here today representing the Orthopedic Surgical Manufacturers Association, OSMA, of which I am Vice President.

OSMA, a trade association of over 30 member companies, welcomes this opportunity to provide general comments at today's Orthopedic Advisory Panel meeting. OSMA's comments should not be taken as an endorsement of the products being discussed today. We ask instead that our comments be considered during today's panel deliberations. These comments represent the careful compilation of member companies' views.

OSMA was formed over 40 years ago and has worked cooperatively with the FDA, the American Academy of Orthopedic Surgeons, the American Society for Testing Materials and other professional medical

societies and standard development bodies. This collaboration has helped to insure that orthopedic medical products are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs.

Association membership currently includes over 30 companies who produce over 85 percent of all orthopedic implants intended for clinical use in the United States.

OSMA has a strong and vested interest in insuring the ongoing availability of safe and effective medical devices. The deliberations of the panel today and the panel's recommendation to the FDA will have a direct bearing on the availability of new products.

We make these comments to remind the panel of the regulatory burden that must be met today. We urge the panel to focus its deliberations on the product safety and effectiveness based on the data provided.

The FDA is responsible for protecting the American public from drugs, devices, food and

cosmetics that are either adulterated or unsafe or ineffective. However, FDA has another role, that to foster innovation.

The Orthopedic Devices Branch is fortunate to have available a staff of qualified reviewers, including Board certified orthopedic surgeon to evaluate the types of applications brought before this panel. The role of this panel is also very important to the analysis of the data in the manufacturer's application and to determine the availability of new and innovative products in the U.S. marketplace.

Those of you on the panel have been selected based on your expertise and training. You also bring the view of practicing clinicians who treat patients with commercially available products.

OSMA is aware that you have received training from the FDA on the law and regulation, and we do not intend to repeat that information today. We do, however, want to emphasize two points that may have a bearing on today's deliberations:

One, reasonable assurance of safety and effectiveness, and

Two, valid scientific evidence.

There is a reasonable assurance that a device is safe when it can be determined that the probable benefits outweigh the probable risks. Some important caveats associated with this oversimplified statement include valid scientific evidence and proper labeling, and that safety data may be generated in the laboratory, in animals and in humans.

There is reasonable assurance that a device is effective when it provides a clinically significant result. Again, labeling and valid scientific evidence play important roles in this determination.

The regulation and the law clearly state that the standard to be met is reasonable assurance of safety and effectiveness. "Reasonable" is defined as moderate, fair, and inexpensive.

The regulation states that well controlled investigations shall be the principal means to generate the data used in the effectiveness determination.

The following principles are cited in the

regulation as being recognized by the scientific community as essential in a well controlled investigation.

One, a study protocol;

Two, method of selecting patients;

Method of observation and recording results;

And, four, comparison of results with control.

The panel has an important job today. You must listen to the data presented by the sponsor, evaluate the FDA presentations, and make a recommendation about the approvability of the sponsor's application.

We speak for many applicants when we ask for your careful consideration. Please keep in mind that the standard is reasonable assurance, balancing the benefits with the risks. The regulatory standard is not proof beyond a shadow of a doubt.

When considering making recommendations for further studies, remember that the FDA takes these recommendations seriously, often as a consensus of the

panel as a whole and they may delay the introduction of a useful product or result in burdensome and expensive additional data collection.

Therefore, you play an important role in reducing the burden of bringing new products that you and your colleagues use in treating patients to the market. Please be thoughtful in weighing the evidence. Remember that the standard is a reasonable assurance of safety and effectiveness and that there is a legally broad range of valid scientific evidence to support the determination.

OSMA thanks the FDA and the panel for the opportunity to speak today. Our association trusts that its comments are taken in the spirit offered, to help the FDA decide whether to make a new product available for use in the U.S. marketplace.

OSMA are present in the audience and are available to answer to answer questions any time during the deliberations today.

Thank you.

PANEL CHAIRPERSON NAIDU: Thank you, Dr. Krasny.

The next presenter is Dr. William Maloney, III.

Dr. Maloney.

DR. MALONEY: Thank you, and good morning.

My name is Bill Maloney, and I'm the professor and Chairman of Orthopedics at Stanford University School of medicine.

And while we're getting up my presentation, I'll do my conflict disclosure. I design hip implants for Zimmer, for which I receive royalties. I am not involved in any surface replacement design. I design knee implants for Wright Medical for which I receive royalties. I do not own stock in any orthopedic implant companies. My travel expenses have been reimbursed by Wright Medical, and currently my time is not being compensated to come here.

So I'm here to make some comments on this submission, and for those of you on the panel who do not know me, in addition to being professor and Chairman of Stanford University, I'm currently Chief of Joint Replacement Service at Stanford.

Prior to this I was the Chief of the Joint Replacement Service at Washington University School of Medicine. I'm a member of the North American Hip Society and International Hip Society. I led the American Joint Replacement Registry effort in trying to get that off the ground in this country and chaired that committee for two years, and I'm currently a member of the Quality Improvement Program for Medicare working with Dr. David Hunt.

I want to say quite clearly what I'm not here to do. I'm not here to indict Smith Nephew. It's a well established orthopedic company, a great reputation. I'm not here to indict Total Resurfacing Arthroplasty or the specific implant, and I'm certainly not here to indict Derek McMinn, who is a colleague of mine and certainly a well known arthroplastic surgeon.

What I am here to do is to make some comments on the study methodology which I think appears to me as a problem, to talk a little bit about conflict of interest. Obviously that's an important thing in this country and one as a chairman of an

academic department at a major medical school I deal with on a regular basis, and make a comment on compelling medical need.

When you look at studies, there are a variety of studies in the orthopedic literature. Most of them are retrospective. There's prospective data collection with retrospective data review, like registry as the Mayo Clinic Registry would be a good example of that.

There's a prospective study. In a prospective study you generate a hypothesis. You design the study to test the hypothesis. You get IRB approval. You recruit patients, and you consent the patients. You collect the data, and you analyze the data.

Then you have an IDE study, which is a prospective study that goes beyond those requirements. There's site monitoring. There's concurring data verification against source documentation. There's adverse event documentation and reporting, and there's FDA inspections, akin to an IRS audit.

When you look at the norms for an IDE

study protocol, these have been well established. The protocol is predetermined. The safety and efficacy endpoints are well defined. The control group is homogeneous with the treatment group. There's well established inclusion and exclusion criteria. There's predefined follow-up intervals and direct patient evaluation. The conclusions are based on a predetermined, valid statistical plan, and there's substantial patient site monitoring which is mandatory.

These trials are usually multi-center under a common protocol. There's contemporaneous accountability for all adverse events and complete documentation of all protocol deviations, regardless of severity.

The data that we're currently or you're currently reviewing in this current PMA submission is a combination of retrospective data and data collected prospectively and reviewed retrospectively. In that submission it states there were not predefined follow-up time windows, standardized clinical evaluations, adverse event report forms or standardized

radiographic evaluations.

So clearly, that doesn't meet the standard that we're used to in the evaluation of Class 3 devices.

When you look at critical study elements, the survivorship data is from a single surgeon. It's from Derek McMinn's data, and the justification of that is as follows. The Oswestry Outcomes Center records information regarding complications, deaths or revisions, but the data is not verifiable. You cannot verify the primary source data. Therefore, the only verifiable data is Dr. McMinn's data.

They further go on to state, "Comparison of data from the Oswestry Outcomes Center database to the data from Mr. McMinn's clinical records provides additional assurance that an accurate, up-to-date survivorship data is known."

But the problem here is "additional." The only data we have here on survivorship that can be verified is Dr. McMinn's data, and it's not done concurrently and not by an independent study monitor.

The single surgeon series, as we all know,

has significant disadvantages. Derek is an expert surgeon. He's been doing this operation since 1989. He is the pioneer in this operation and deserves a lot of credit, but the question is: were his results be optimal to the surgeon community at the U.S. at large?

Clearly, I don't think that's the case. This does not represent U.S. surgeon data or U.S. patients, and this is a new operation in the United States. We have no experience with it, and surgical training is going to be critical.

When we look at the specific cohorts in this study, there are three. There's an X-ray cohort. There's the Oswestry cohort, and there's the McMinn cohort.

The Oswestry Outcome Center, which it's unclear how that's funded, is a self-administered patient questionnaire. There's no direct patient contact, which is, of course, required in ID studies. They report an outcome measure which we're not familiar with, an OSHIP score which appears to be a combination of a Harris HIP score and a Merle D'Aubigne score, and presumably there's patient

consent in this study, although it's not well documented.

In the McMinn cohort, it appears to have no functional outcome data. It is specifically just survivor data, as the outcome data was not available for review of this submission, and it doesn't appear that those patients in the McMinn cohort were actually consented for a research study.

They certainly were consented for surgery. The PMA submission clearly states that they were given options as it relates to hip arthroplasty, but that's fundamentally different than being consented for a research study.

What about the radiographic analysis? This, again, appears to be primarily a retrospective radiographic analysis. Clearly at the beginning of this PMA station they stated that there's no radiographic protocol.

If you look at the numbers in this cohort, there's 124 hips. Two hips were excluded because of patient death in one patient. Four hips were revised. So they left with 118. Ten of those we then lost to

follow-up. So you're down to 108, and then 19 hips had no immediately post-op X-ray. So there's 89 hips which were potentially valuable.

It goes on to state there were immediate post op films on 89 of 108 procedures with five radiographs, but the sponsor stated that these films were of low quality, portable films and unusable for the purposes of precise postoperative comparisons.

Therefore, baseline films for the purpose of comparisons were made in each of the 108 cases in the postoperative time period, usually within three months, but eight of the 108 procedures had baseline evaluations performed at the time points ranging from 110 to 860 days.

So in some cases the baseline X-rays were quite a bit of time after the index procedure. In a prospective IDE study, these would all be protocol violations and could be potentially excluded. So you could actually end up with a cohort in the X-ray study of zero if you had a strict analysis of the data.

The next topic I want to briefly discuss, and it has already been a significant topic here this

morning is one of conflict of interest. In this country, we are under great scrutiny as it relates to our conflict, and as a department chairman, again, I deal with this on a regular basis.

Conflict of interest exists when an investigator and/or his or her family has the potential for financial gain. Financial conflicts in human subject research at least at our institution are of special concern, and I'm sure they are across this country.

How, Derek is the product designer. He's the pioneer here, and he's one of the co-founders of Midland Medical Technology, who we do not have disclosure in the PMA submission as to what the exact conflict is here. This company was purchased by Smith and Nephew for 67 million pounds, and that's a fair sum of money in anybody hands, and it will pay another 33 million pounds for the Food and Drug Administration or if the Food and Drug Administration allows this procedure into the United States.

The company's history, this has been an extremely successful company, and I wish I was

involved with it. It was incorporated in 1996, and in 1997 they issued about 100,000 shares, 60,000 of which were immediately transferred to Sky Fall, Limited and 30,000 to Maldeney, Limited. Who owns those we have no idea, and who has gotten the 66 million pounds needs to be addressed because we have to do that in this country, and the playing field needs to be level.

Now, Derek has got a five-year contract based on the Daily Mail with his new employers. He told the Daily Mail, "I will stay on until I retire and drop. I am completely addicted to this product."

Now, if that's the case, if he's an employer of the sponsor, and again, we need to have clarification there, it appears that the data in this PMA is entirely from the clinical practice of a Smith & Nephew employee.

In this country and for the FDA for the IDE studies, you rely primarily on the individual's IRB to oversee issues of patient protection. This includes the study consent form and disclosure of financial conflict of interest.

At my institution I would not be able to

do an IDE study that involved a Zimmer product. I would not be able to do a clinical study that involved a Zimmer hip product. It's simply not mitigatable.

The academic community in this country has weighed in on this issue. The NIH has weighed in on this issue, and the federal government has weighed in on this issue. Significant financial conflicts cannot be mitigated. It doesn't mean that the data is bad, and it doesn't mean that the investigator is dishonest. It just means that the appearance of significant financial conflicts currently are not felt to be mitigatable.

The last point relates to compelling medical need. Now, some people have said, well, these products are great, we need to have them on the market, but clearly with resurfacing arthroplasty that's not the case. Conventional hip replacement is a good operation. It has an extremely long track record, and currently in this country there are three IDEs being performed and two PMAs that are pending before the FDA.

Corin and DePuy and Wright Medical all

have IDE studies in this country. So clearly, we're going to have a little bit higher quality data to review in the relatively near future.

So how do I summarize my evaluation and those of us who are involved in the American Joint Replacement Registry?

This is a PMA device. It's the first of its kind in the United States. It's supported by data, and this is a quote from the PMA submission, from essentially one surgeon, Derek McMinn, who is a very qualified surgeon and very expert surgeon.

That source of data is also the product designer and the founder of the company and the things they implant. IDE conventions are not followed. The data set does not reflect the high bar set by the FDA for approval of Class III orthopedic devices, and I remind you that the last time this type of data was accepted at least that I could find was back when the Mittelmeier hip was approved. This was a ceramic-on-ceramic total hip replacement that had excellent clinical results in Europe, principally by Dr. Mittelmeier. There was no U.S. IDE. It was a

clinical disaster in this country, and it doomed ceramic-to-ceramic hip replacements in this country for years.

This would be precedent setting in terms of how all Class III devices are evaluated for approval in this country, and I'll tell you I was involved, and I was in the orthopedic implant side. If this goes forward, this would be the last IDE done in this country. There's no reason to do an IDE if retrospective data from another country is acceptable.

And maybe that's the way we should go, but clearly, it's a significant change in our current standards. Maybe the bar is too high, and maybe it is too burdensome, and it probably is, and I probably need to have some changes made, but this is a big jump from what we're currently used to, and it potentially is a significant patient safety issue.

Thank you for your attention.

PANEL CHAIRPERSON NAIDU: Thank you, Dr. Maloney.

Is there anyone else in the room who would like to address the panel at this point? If so,

please raise your hand and come forward and state your name, affiliation and whether you have any involvement in a medical device firm.

(No response.)

PANEL CHAIRPERSON NAIDU: I don't see anyone. Please note that there will be a second open public session in the afternoon. If anyone else would like to address the panel about today's agenda topic, you may speak in the afternoon.

We will now proceed to the sponsor presentation for the Birmingham hip resurfacing device. We will then have a short break and proceed with the FDA presentation.

After lunch the panel will deliberate on the approvability of the PMA. Before the panel votes on the approvability of the PMA, there will be a second open public hearing and FDA and sponsor summations.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the

panel.

We will begin with the sponsored presentation. The first Smith & Nephew presenter is Mr. Marcos Velez-Duran, Vice President of Clinical and Regulatory Affairs and Quality Assurance. He will introduce the other Smith and Nephew presenters.

Mr. Duran.

MR. VELEZ-DURAN: Yes. Good morning. My name is Marcos Velez-Duran, and I am the VP of Regulatory and Clinical Affairs and Quality for Smith & Nephew. I'm here today to present to you a summary of the data presented in the pre-market approval for the Birmingham hip resurfacing product.

I will take this opportunity to thank the panel and FDA for the time and effort that they have put in into the review of this PMA. In particular, I would like to thank FDA for embracing the spirit of the regulation. As demonstrated by the then interactively review in this PMA and concerning the data that will be presented today as meeting the requirement of valid scientific evidence as outlined under the law.

The presenters for this morning as me, Marcos Velez; Mr. Derek McMinn will present design history; Mr. Tim Band will present on preclinical information. I will come back and present the summary of the clinical data. George DeMuth will present on the statistical issues associate with this PMA and data analysis, and Neal Defibaugh will review the labeling, plus approval studies and plan for training.

In addition, we have a number of people supporting our efforts today that will get up and answer questions as necessary, that is, Dr. Cecil Rorabeck, Professor James Richard from the Oswestry Center, Mr. Joseph Daniels, Professor Anthony Unsworth, Dr. Roger Rogerson, Marie Marlow, Dr. Marc Thomas, and Sally Maher.

Now I would like to introduce Mr. McMinn to give the next presentation.

DR. McMINN: Thank you, Marcos.

Good morning, ladies and gentlemen. I'm Derek McMinn. I'm an orthopedic surgeon from Birmingham, England, and I'm the co-inventor of the Birmingham hip resurfacing. I do have a financial

interest in the Birmingham hip resurfacing. I'm a consultant for Smith & Nephew, and I'm a non-Executive Director of Smith & Nephew.

For the nonclinicians, I just want to do a very quick review of the indications for hip arthroplasty. On the left there you see a normal hip, and on the right you can see an osteoarthritic hip with loss of some articular cartilage.

Next.

When you look at an arthritic femoral head, there is the retained cartilage, and there is the variable on the femoral head. So the difference between a pain free hip and a very painful hip with a disabled patient is the loss of a few millimeters of articular cartilage.

Now, for that lesion, we take a really aggressive approach to it. We resect the femoral head and neck, insert a cup in the stem to the shaft of the femur called a total hip replacement. Why do we do that? Because we've all been trained to do it and because for the vast majority of patients it works extremely well.

Next.

Here's a patient of mine, a total hip replacement freshly done on the left. A few years later unfortunately the patient has developed loosening of the femoral component with substitutes. It had to be revised.

Next.

This is another patient of mine with two hip replacements and both sides have failed for different reasons. On this side, a typical total hip replacement. Where is the polyethylene, and that is caused a linear pattern of osteolysis and loosening of the socket.

On the other side we've got a hybrid total hip replacement and an uncemented cup, and again, there's been wear of the polyethylene, and this patient has nasty pelvic osteolysis, and on the femur side it's removed most of Zone 7 in the femur.

The problem that we all face now is largely that set-up with pelvic osteolysis thanks to wear of polyethylene, and the problem is made worse the younger and more active the patient is.

Next.

So to summarize the problems with total hip replacement, there's an incidence of dislocation. In our country it's three to four percent. There's a leg lengthening issue with total hip replacement, which is a common cause for patient unhappiness. There's acetabular and femoral loosening which is reducing with time, but particularly acetabular and femoral osteolysis is a big problem. There's the inevitable stress shielding of inserting a stem into the shaft of the femur and a revision surgery, as we all know, is difficult and expensive and in young patients may be recurrent.

So why can't we just replace the worn out acetabular and femoral articular cartilage? The answer is we can, and that's a typical model for a hip resurfacing where we put a thin shell over the ball and a thin shell into the socket to replace the worn out articular cartilage.

Is that new? Not at all. This was Sir John Charnley's first attempt at hip arthroplasty, and he used Teflon shells both on the socket and the

femoral head, and here's some removed two years with complete wear through of the socket and the head.

Then came the 1970s generation of his resurfacings using the materials available at that time, polyethylene on the socket, metal shell on the femoral head.

Here's a case of ours, loose cup, a common complication of these cemented resurfacing models.

Here's another one I revised, loose socket, femoral component solid. When we sliced that component there are holes in the femoral head. Why are they there?

Here you can see an entry hole at the head-neck junction.

Next.

Here you can see a granuloma on histology and on polarized light microscopy this head is stuffed full of polyethylene debris. So the polyethylene debris problem has loosened the cup, and it's starting to erode the femoral head.

Is hip resurfacing new in the United States? Not at all. There's some extremely good

innovators in the United States. The first two models of hip resurfacing are cemented, and the problems are largely as I outlined already in the previous models.

The second two models are uncemented, and they did, indeed, address the issue satisfactorily of component loosening. But of course, as you can see from those sample radiographs, they did not address the problem of tremendous osteolysis because of polyethylene debris generated as an inevitable result of the large head articulating on polyethylene.

So to summarize the 1970s and '80s resurfacing, there's a small instance of femoral neck fracture and collapsed femoral heads. That was manageable. It wouldn't have finished resurfacing in the '70s and '80s. The thing that finished it was the large head articulating on polyethylene gave massive debris of polyethylene, and that loosened cemented cups and cause osteolysis with cementless components.

So the conclusion of that was that hip resurfacing was not a viable operation with varying materials available at the time. Our experience in Birmingham with the '70s and '80s resurfacings

unfortunately was no better than anyone else's, and this is a survivorship curve with the cases we did, and you can see that we've got a 50 percent revision rate at six to seven years.

As a trainee I put some of these in, and then as an orthopedic surgeon in the late '80s, I got to revise most of these cases. So I was seeing patients turning up in my clinics with resurfacings that had failed because of polyethylene debris generated from large femoral heads.

Also in my clinics, I was following up my predecessor's cases of metal-metal total hip replacements, and the first total hip replacement of a metal-metal nature in our hospital was done in 1966. So I was seeing large headed implants, metal-metal, that were surviving well over 20 years.

To summarize the metal-metal total hip replacement experience in use sine 1960, osteolysis is rare and severe osteolysis is exceedingly rare. Peter Walker showed a few decades ago that equatorial bearing must be avoided. Polar bearings work well, and large heads work well.

There you can see the difference between an equatorial bearing with the head jamming with increasing load and the successful polar bearing where the ball is slightly smaller than the inside of the cup.

Now, it eventually dawned on me that what we needed to do to resurrect hip resurfacing as a viable operation was to take the concept of resurfacing and put with it the large headed metal-metal that had been clinically proven since 1960. And interestingly, that thought didn't just occur to me. It occurred also to the late Professor Heintz Wagner from Germany, and without knowing what each other was up to, we ended up both putting in our first metal-metal hip resurfacings in February 1991.

So to summarize our first six years' experience with metal-metal, we started with a loosening problem. We then had to change the component design, but cementless fixation of the socket was best. Cemented fixation of the femoral head was best.

The operation eventually was extremely

reliable. Hip function was good, and it satisfied all of those goals that we had talked about in the '70s, namely that where failure occurred revision to a total hip replacement was easy because the femoral canal was not violated.

We had three cups available in those early systems. There are now 23 cups available in the Birmingham hip resurfacing system, and we designed that and this first use was 1997. The implant has a porous surface on the cup with a hydroxyapatite coating.

And there you can see a single layer of beads integrally cast with the substrate metal, and that means that you don't have to heat the implant by centering to glue on the beads. That has two effects. The beads are highly unlikely to come off, and second, because it's not subjected to the heat of centering it does not destroy the carbide microstructure of the metal, which you can clearly see and which we believe is very important for satisfactory metal-metal long-term bearing performance.

This is a case that I had to remove for hematogenous infection a number of years after implantation, and you can see excellent bone ingrowth and on growth onto that socket.

This is another case, and you can see good ingrowth into the porous surface. So this device appears to be acting as intended.

On the femoral side, we've gone for a cemented component because that's what I've done for the last 13 and a half years, and that's, therefore, what we did with the Birmingham resurfacing.

On the femur, we've got microinterlock of Cancellous bone into the peripheral femoral head bone and a cementless stem. So we have a specific design to line-to-line contact of implant on bone, and as the implant is inserted, the high pressure drives low viscosity cement into the peripheral femoral head giving good microinterlock in succession.

On the right I'm not sure if you can see it, but that's blown up in an attempt to show you that that's a tapered stem put into a parallel hole, and from this point down the stem has a gap between it and

the bone, and I did that deliberately to try and avoid distal loading and proximal stress healing of the implant.

This is the first Birmingham hip resurfacing that I carried out, that was carried out ever on the 30th of July 1997 in a 38 year old man. I can't quite read it from there. That is his postop X-ray, one year and two-year X-ray.

Next.

Five-year X-ray. Now, what can we tell from this and other X-rays? Well, he's got no heterotopic ossification. He's got no radiolucent lines. That's not too surprising. Bach's radiographic study published from Melvin in the Journal of Bone and Joint Surgery showed that they had no radiolucent lines.

There's no gross migration of this component, but what about minor migration? Because we know from our Swedish colleagues that early minor migration can herald late loosening. Can we tell about minor migration from a plain X-ray with an accuracy of plus-minus three millimeters? No.

Can we tell about stress shielding? No, because you need a 30 percent change in bone density to be able to see it on a plain x-ray. So we need special studies. So we've done the RSA with our Swedish colleagues from the Carl Linsek Institute in Stockholm, and there's also been an RSA study published in the Journal of Bone and Joint Surgery also from Oxford, England.

And on the femoral side, there is no measurable migration out to two years. On the acetabular side, there's .2 millimeters of migration of the socket within the first two months, and then there's no further migration out to two years.

If we're looking at density, we need to do a longitudinal Dexter study. This has been done by Kishita (phonetic) and again published in the Journal of Bone and Joint Surgery, and his control group was a standard proximate porous coated cementless stem, and on the cementless stem the bone density in Zone 7 goes down. That's what we all expect.

Interestingly, with the Birmingham resurfacing in Zone 7, the bone density goes up. So

not only are we retaining bone in the femur, but when we load that femoral head normally in the absence of pain, the density in the upper femur goes up.

So hip resurfacing is not new. Metal-metal total hip replacement is not new. The new thing is combining metal-metal with resurfacing.

Now, all we need to know is: is the metal line exposure to patients from a metal-metal Birmingham hip resurfacing any different to a contemporary metal-metal total hip replacement?

We've done a number of studies. We've included some of these for your interest. This is whole blood cobalt analyzed by high resolution ICP mass spec, which is the most accurate means we have of measuring these.

In our one-year Birminghams, with 50 and 54 heads, the levels and mean and standard deviations are shown. The one year metasuls are shown, and they were 28 millimeter heads and the five-year Birminghams are show, and there's no difference between the large headed Birmingham metal-metal, and the 28 millimeter metasul metal-metal.

For chromium, again, there's no difference between the large headed Birminghams and the 28 millimeter metasuls.

Now, we were interested in the total amount of metal lines produced. So we've got 24-hour output of cobalt on a lot of patients, and here is a longitudinal study of the Birminghams at two years, and the amount of metal line produced per day in the Birmingham with a 50 and 54 head is no different to the metal line produced in the 28 millimeter metasuls.

At five year the Birminghams metal line production is no different to the 28 millimeter metasul production.

So to summarize, hip resurfacing is not new. Metal-metal total hip replacement is not new. With the new part of combining metal-metal with resurfacing, I've shown you that fixation of the femur and the acetabular component of the Birmingham hip resurfacing is good as demonstrated by two published RSA studies in the Journal of Bone and Joint Surgery. The loading of the proximal femur is favorable as judged by DEXA and, again, published in the Journal of

Bone and Joint Surgery.

I've just shown you that the metal line exposure to patients is no different with a metal-metal Birmingham hip resurfacing compared to a 28 millimeter headed metasul bearing total hip replacement.

So the conclusion is that the Birmingham resurfacing device is based upon the lessons learned from previous resurfacing designs and historic metal-metal bearings.

Thank you.

I'd now like to pass over to Tim Band, who was a young, fresh faced metallurgist when I first met him, but I've grown him then by totally unreasonable demands in the last ten years.

MR. BAND: Thank you, Derek.

Good morning. My name is Tim Band. I'm an employee of Smith & Nephew. I'm going to present on the device description and preclinical testing.

Before I do that, with the Chairman's permission, I'd like to present the panel with a physical example of the component for your physical

consideration.

PANEL CHAIRPERSON NAIDU: That would be great. Thank you.

MR. BAND: The Birmingham hip resurfacing device, as we've heard, is a device comprising of two components, the femoral head and acetabular cup. Both components are produced by high carbon cast cobalt chromium material. The femoral head is available in six sizes of four millimeter increments. These are described by the external diameter of the femoral component and are in sizes between 38 millimeters and 58 millimeters.

The femoral head achieves fixation and stability through the use of bone cement, and on the inside of the femoral head, there are six recesses to assist in the stability.

There are 12 sizes of acetabular cup which means there are two sizes of cup per femoral head component. Again, they're described by their external diameter, and they start from 42 millimeters in diameter through to 66 millimeters.

So, for example, for a 38 millimeter

femoral head component, you could use either a 44 or a 46 millimeter diameter acetabular cup in the event of any mismatch between the femoral device and the recently prepared acetabular.

The acetabular cup is a porous coated, HA coated, cementless device, and they're also a dysplasia option and bridging cup with screws to provide primary stability.

So to summarize the technical characteristics of this system, we can say that the material is a high carbon, as cast cobalt chromium material. The specification for the components allows the femoral head to be smaller than the acetabular cup to provide a polar bearing, as described by Mr. McMinn in his lessons learned presentation.

As I showed you, the range of devices I described are appropriate to meet the anatomical sizes of presenting patients. The acetabular cup is an uncemented HA porous coated device, and the femoral component achieves stability with the six recesses inside the femoral head and the use of bone cement.

So both components are produced from

cobalt chrome molybdenum alloy conforming to ASTM F-75, an ISO 5832 specifications. And the biocompatibility of this material has been proven by its benign clinical use since as early as the 1930s.

The first specification for this material grade and composition was actually described in the early 1960s, but interestingly the material grade has remained fairly unchanged to the present day.

So on the slide here you can see an example of a first generation metal-metal bearing which had survived for over 30 years in vivo. Its failure mode was typical of this type of device, which was for tissue growth around the smooth cobalt chrome surface.

We know, of course, today that this is not a very good fixation surface, but the slide on the right is a micrograph. This is a section of the component which has then been polished and chemically etched to reveal the metallurgical phases in the microscope here.

And as we can see, it's a biphasic material, which means there are two microstructural

phases in the material. The light background is the matrix, which is essentially cobalt, chrome, and molybdenum maximums, and the small, dark particulate component is a precipitate carbide which is made of chromium and molybdenum carbide, which forms during the solidification of this alloy during the investment casting process.

The Birmingham hip resurfacing which is shown below has its microstructure shown on the right-hand side, and as you can see, its specification was based upon the extensive forensic study of those first generation metal-metal bearings. The microstructures are comparable.

So to talk about our preclinical studies which were submitted to the FDA and summaries have been made in your panel packs, all of the studies were conducted in accordance with the FDA guidance documents and were provided for the components, the beaded surface and the HA coating. The component testing included wear testing, friction testing, femoral standard fatigue testing and kinematics were assessed by simulating range of motion.

Metallographic microstructure metrology examinations were also carried out to characterize the device.

The preclinical studies carried out on the beaded surface included static shear, shear fatigue and static tensile strength testing, while on the substrate yield ultimate tensile elongation and abrasion testing were carried out.

Finally, the preclinical studies on the hydroxylapatite coating included environmental stability, coating thickness, static shear and tensile strength, and analysis of the chemical and crystallographic characteristics of the coating.

So, in summary, the device which was designed from the lessons learned that Mr. McMinn presented in his earlier presentation have all been evaluated on the preclinical data, and the results confirm that the device showed performance intended in vivo.

Thank you.

I'd now like to hand over to my colleague, Mr. Marcos Velez-Duran.

MR. VELEZ-DURAN: Marcos Velez-Duran with

Smith & Nephew, and I'm to present the summary of the clinical data and clinical studies.

This product was first available in Europe in the U.K. specifically in July of 1997. Since then it has been currently marked in 23 countries. Some of those countries include Canada, Australia, Japan, and all over Europe.

There have been more than 33,000 implants implanted worldwide at the time of the PMA submission.

The evidence of safety and effectiveness presented in this PMA is based on a consecutive series of 2,385 cases, surgeries that occur from July of 1997 to 2004. The safety data that's presented in the PMA, and you have available in your packet, is a review of all 2,385 cases in this study. The effectiveness data is based on a total of the first consecutive series of 1,626.

The effectiveness data is based on an independent review and follow-up by the Oswestry Center Registry, and those are surgeries from July 1997 to March of 2002.

The radiographic study that you also have

in your packet is based on a total of 124 cases. Those are the first consecutive 124 cases conducted by Mr. McMinn.

The study design has been described as prospective, and it's a consecutive series of like I mentioned, 2,385 procedures on the BHR, and no further design changes are in the series. So 100 percent of the products in this series are of the same design.

It's a single center by surgeries conducted by Mr. Derek McMinn and their Birmingham hospital using a proven surgical technique.

There is five years' follow-up on the series, and we include safety, survivorship, pain or function assessment, and also patient satisfaction.

The strength of this data is that one is consecutive clinical series, and for the safety assessment there was a 100 percent audit of all cases at patient records and at the Oswestry Center.

On the effectiveness side, the prospective registry was independent of Mr. McMinn, was performed by the Oswestry Outcomes Center and include, like I mentioned previously, 1,626 cases, and in addition to

the patient self-assessment of pain and function, there is also a patient satisfaction question.

Also, as part of effectiveness, there's an independent radiographic evaluation at five years using a prospective protocol on 124 cases.

There have been some questions about the comparability of the U.K. and the U.S. in terms of patient populations and practice of medicine, and we will surely talk about this later in this meeting. Our observation is that there are similar target populations in both countries, and joint surgeries are performed in the same matter in both countries and similar in hospital procedures.

There are three specific cohorts that are mentioned in the PMA. There is the X-ray cohort, Oswestry cohort, and McMinn cohort. I would like to make the clarification that they're all related to the very same patient, the total of 2,385 cases. It just happened that the X-ray cohort and the Oswestry cohort were patients that were followed by the Oswestry Center registry, but all three cohorts were included in the safety data.

The effectiveness measurement, the primary effectiveness measure for this PMA, incident by survivorship and secondary effectiveness measures include the Oswestry modified Harris Hip Score, which we will refer to through the presentation as OSHIP patient satisfaction.

In addition, there is the five-year radiographic assessment.

Safety measures include the primary safety measure is the number of revisions and percentage of the population study, as well as all other adverse events.

The study population of these cases include mostly men with osteoarthritis.

In terms of accountability, we have an excellent patient follow-up at five years of 90.8 percent, and at five-year survivorship of 98.4 percent. The survivorship is also available and is consistent with publish reports in British Journal of Bone and Joint. You can see series from Australia, other parts of Europe and also U.K. The survivorship estimate is consistent to the one we observe in this

PMA.

In addition, the Oswestry Center followed a total of 5,000 cases, including Mr. McMinn. So 140 surgeons collected 3,374 cases in over five years, a maximum of five years to survivorship is 96.3 percent. So it is consistent with what we see with Mr. McMinn. So the success, other clinicians are able to repeat the same success.

In terms of clinician rates as compared to a comparative group presented in the PMA for the BHR on all cohorts or the specific group that's X-ray, Oswestry cohort, it's the primary population group for effectiveness. You can see that the percent of revision for BHR compares very well with published articles on existing total hip replacements.

The Oswestry modified Harris Hip Score was developed by the Oswestry Outcomes Center. It is validated and compares well to the Harris Hip Score. It's a patient self-assessment of pain and function, and it took questions and scored similar to the Harris Hip Score, with a difference that flexion and extension questions are different from the Harris Hip

Score in that the OSHIP score asks relevant questions to patients and activity of daily living.

There's also patient self-assessment of satisfaction that's very simple and we will present it later in this presentation.

To compare the Harris Hip Score to the Oswestry hip score, I put together the two scoring systems, and as you can notice, the only difference is in the section of shoes and socks and deformity and range of motion. Those have been captured in the Oswestry score in the area of movement, and it equals 13 points. So at the end of the day both scoring systems are up to 100 points.

The result of the OSHIP scores is as follows. There is a baseline. There is an outreach of 59.8 points and at five years, 95 points, a significant improvement over time.

And if you were to define success based on the scoring system as patients that have greater than or equal to 80 points at five years, 93.2 percent of those patients are considered successful. Even if we were to define success on the total score as greater

than or equal to 90 points, at five years our success rate would be 85.5 percent.

The second, in the patient satisfaction, these are the questions that were asked of the patients. You can see they're very straightforward questions, no room for misinterpretation of the question.

And at five years, patient satisfaction was 99.5 percent of extremely pleased or pleased with the operations.

On the radiographic data, there were predefined failure and success criteria. The predefined failure criteria is presented here as presence of the incomplete or complete radiolucencies or a radiolucency in all zones and migration of components greater than two millimeters or a change in acetabular orientation of greater than or equal to five degrees.

The five-year radiographic success result is 97.2 percent. There were three out of the 108 that were radiographic failures, representative of 2.8 percent, and we want to note that no radiographic

failure in the series studied in revision.

Those radiographic findings are consistent with what Mr. McMinn presented previously on RSA studies, which are the best ways of assessing migration and other radiographic observations.

The primary safety outcome with revision and of the total, 2,385 cases there were 27 revisions and probably as previously explained, that represented 1.1 percent of the total population. The majority of the revisions were on the femoral neck fracture, and they occurred as we can see by the average time to revision, early, followed by infection and collapsible head, which happen between two and three years on an average.

We wanted to spend a little time explaining the method of data collection for our first event. We collected all first events in patient charts and the OSHIP questionnaires. There was no differentiation at the time of the collection between clinical observation and actual event. The collection of the adverse event was conducted by separate consulting group. Mr. McMinn was not included in that

assessment or review of the chart.

Some hips have more than one adverse event over time, and adverse event documented multiple times were treated as separate events. It was a very comprehensive review of everything that was in the patient chart.

In terms of result and device related events for the overall cohort, the AVN, actually all of the device related events were at one percent or less. For AVN, there's one percent for which were at grade the one year post op, and 31 out of the 35 total observations of AVN were interoperative observations.

On the femoral hip collapse, there were 15 total reported events. Eight were evacuated. Seven were interoperative observations, again, femoral neck fractures less than one percent, component migration less than one percent.

In summary, we have a very large series of hips, 2,305, followed for a long term, a long-term follow-up for five years. Excellent patient follow-up of 90.8 percent at five years.

There's an independent assessment of pain

and function by a separate research center that was presented and not related to Mr. McMinn. There's an assessment of patient satisfaction, independent critique or evaluation, confirmation of the PMA there resolved by other BHR series, and literature result for a total hip replacement.

In the effectiveness side, the survivorship was 98.4 at five years. The Oswestry score was an average of 95 at five years; patient satisfaction, 99.5, or extremely pleased with the operation at five years; radiographic evaluation, 99.2 success at five years. In terms of safety, revisions are 27, which represent only 1.13 percent of the total population and very low instance of the adverse event, like I mentioned, all of them less than or equal to one percent.

In conclusion, we have talked before in the presentations before me that the BHR device design was based upon the lessons learned from previous resurfacing design and historical metal-on-metal bearings; that the clinical data confirms that the device should perform as is intended in vivo, and now

the clinical data offer a reasonable assurance of safety and effectiveness.

Thank you.

George.

MR. DeMUTH: Hello. I'm George DeMuth. I'm a consultant to Smith & Nephew, and I do not have an interest, financial interest, in the product or the company.

So I'm going to provide some statistical commentary and go to the next slide.

I had a few background comments, and then I want to touch on the accountability and efficacy in terms of surviving OSHIP and have some conclusions. Go ahead.

I want to just start with some interpretational issues and we'll come back to them later, but the OSHIP has actually been collected prospectively, but we're analyzing it down the way now, and that constitutes some independent follow-up, but we do have the single site issue and trying to figure out what to compare against, which is part of what I think the discussion will be today.

The FDA raised questions about pooling of the data. My first reaction was it's a single site, single physician. People are being handled the same way. So I'd like to be inclusive, but it's also of interest to see if we can see if some of the subsets of patients are behaving differently. They're better or worse than expected.

And I want to take this as a brief note to thank the FDA because they provide some nice commentary and, I think, added to the analysis.

So the data I'm going to present will actually be for unilateral hips in the common tables. I don't have an n here. It was actually more than 1,100, and it will be the X-ray and Oswestry cohorts.

Go to the next slide.

And the reason I want to do the X-ray and Oswestry cohorts is because there we have the data follow-up coming off the OSHIP data and we can use that for censoring. So in this case we know we've gotten contact from the patient and have a much better feel for whether they, you know, are being aware or we know what they're doing, and for the McMinn cohort,

those patients we would have to use a cutoff date, and that would be conservative.

So we'll focus on the group that we know the best about.

Go ahead.

All right. So this is actually the OSHIP thing. I want to start and talk about here on the bottom of the slide because in terms of survival we want to know what their last visit is, and they may have some intermediate missing OSHIP data, but we want to know at the end how they're doing.

So we had a very nice, 91 percent follow-up at five years across the cohorts, and very good, 88, greater than 85 percent three and four. So I think in terms of survival in that kind of follow-up we're very happy about the data.

Now, there's some missing data at the one and two year data on the OSHIP insert, some missing baseline that doesn't show up here as well, and so in terms of evaluating the OSHIP, we have to have that in mind.

Now, sort of back up to the top, there

wasn't a flag in the Oswestry Outcomes Center that said patients were discontinued. So what we did is just to try to get some idea. That was to look at whether patients had missed their last two expected visits, and that doesn't even mean that they won't come back in, but in this case, it was 84 out of the 1,626 hips. That's just slightly more than five percent.

So I think in terms of the survival endpoint, that's good as well. So let's go ahead.

I don't want to spend a lot of time here, but this just a report. Really the rate here for this cohort, the unilateral X-ray and Oswestry cohorts: 98.3 percent survival, 1.7 percent revision rate. The upper bound is 3.1 percent of revision rate. So it looks solid as we expect with a lot of patients.

So let's go.

So without trying to do some of these covariate analyses, I think there will be some discussion later about P values. I'm just presenting both here. None of these are significant for the cohort and the gender and the age at five years.

There's, you know, a very small survival difference.

I wanted to pick up and just look at the baseline data, people that had baseline and didn't. It's not different, but the people that didn't have baseline available were just slightly worse, 1.7 percent -- 1.3 percent. Sorry.

Let's go ahead.

We looked at the diagnosis. This is the reason for resurfacing. We saw a significant or marginally significant effect for AVN. Nothing else was different. All of these P values are pair-wise comparisons of the osteoarthritis group. So I don't think that's an unexpected result.

Let's continue.

This just shows the all hips, unilateral versus bilateral. Bilateral is still a little bit better, but again, good across the board.

Go ahead.

So the X-ray and Oswestry cohort, I think, is a good focus here. It's the best follow-up information we have, and it looks very good in terms of the data, the file we have and the revision rates,

less than two percent at five years, 3.1 percent upper bound.

There's a limited number of revisions. Probably doesn't have a lot of power to see subgroup effects, and there was one significant effect in terms of AVN.

So go ahead.

This is the OSHIP data, and this is observed data, and I don't want to spend long here because you've seen it, but a big increase from 60 to mid-90s. That's basically on average 35 to 36 points as an increase, and it's just very large. So let's go to the next slide.

I think this probably to me is a little bit better because you see the majority of patients less than 70, and then everybody is piled up to be greater than 90 or greater than 80. So it looks like you have a very strong response in the OSHIP.

And so this summary is just a big response, a good response for five years.

We did model the OSHIP two-plus year results. That's basically figuring if they had a two-

year point, you took that one or you took the next one after it. Almost everybody has that, and there were some significant effects there. I think we just have a lot of power because now we're talking about, you know, 1,100 hips and effects on the order of three points, you know, would be significant, three to four points.

And in terms of a 35 point increase, I'm not sure that we have to worry about that a lot.

So if you touch on this missing data issue back here, a couple of cuts of it and a couple of ways to look at it. One, it summarized patients that had missing baseline, looked at their post treatment, and you just compared that. You wrote sort of descriptively to the other patients. Those differences are less than three points, around two points, indicates that those patients may have had a slightly lower mean.

Didn't repeat a measured mile, but there's very little difference there, but that's probably dominated by the observed data.

And then the other point is that if you

look at the two-plus data, it looks like, again, that has very high value. So I don't think you can rule out an association here, but it looks small in respect to the big improvement we're seeing on the average.

Let's go ahead.

This is just patients and just to point out and we saw it before; all most everybody is pleased, and this coincides with high survival, low revision rates and the very big improvement in OSHIP.

So let's go ahead.

This is going to touch back. I hope to capture here a compendium of the issues that will be raised later on about the study design, a single investigator, no control. There are no a priori sample size. I think some of these I answered, and then we have a very large sample size. I think the OSHIP was very sensitive to reasonably small differences relative to the treatment size.

I think we had very good follow-up in that. We got very tight confidence bounds around the survival. I think the survival is a very objective endpoint here, and so I think that's favorable.

We have external radiographic review. It helps, I think that the efficacy data is being collected in terms of OSHIP externally and an independent safety review. So I think it's important to put this study sort of in the context of the other studies that we had, the published literature where we see similar survival rates and nice or, you know, high survival rates and high OSHIP satisfaction look internally consistent.

So second page.

There aren't too many comments about this. There is a question about the study design for the validation work, and I don't have too many comments. Just say there were some usually high correlations. There was a difference in the mean OSHIP and HHS. At least it's in the direction that the OSHIP is lower, which would make it seem more conservative.

I think, too, we have to go back and look at OSHIP in terms of patient satisfaction, that consistency as well.

All right. Go ahead.

So in summary, back to sort of what I

thought were data points here, there's a large number of procedures. We have, I think, very good follow-up. Survival rate in the X-ray and Oswestry cohort for the hips of 83. -- 98.3 percent, sorry. Large OSHIP improvements. Patient satisfaction look very good, and to the extent we did a sensitivity analysis, our evaluations of the missing baseline data, missing data don't lead me to believe it should interfere with a major interpretation of a very large increase from baseline.

This brings me back to the slide we've been building on. I think we've started with the lessons learned, and there's a history about how the device is what it is and how we should have expectations of good survival for this device. In the preclinical data, overview of the clinical data and now some statistical analyses showing, you know, very good effects and a lot of data with good follow-up.

So I'll turn it back to Neal.

Thanks very much.

MR. DEFIBAUGH: Hello. My name is Neal Defibaugh, and I'm an employee of Smith & Nephew.

I would like to spend just a few minutes talking about some approval considerations, namely our proposed labeling, training and post approval study.

Next slide, please.

We believe the data that we have shown you today demonstrates that the BHR device is intended or can be used for patients who are at risk of requiring more than one hip joint replacement over their lifetimes, and while it's impossible to predict exactly who may require a future revisions, some factors that are known to increase the risk of revision or include patients of a young age and anybody less than 55 years and/or high activity level.

Next slide, please.

Therefore, specific indications for use that we believe the data supports include noninflammatory degenerative joint disease such as osteoarthritis, AVN, dysplasia, DDH, as well as inflammatory DJD, such as rheumatoid arthritis.

Next slide please.

Obviously there are contraindications to the use of the BHR device. General complications you

would see for any type of hip replacement include things like infection, patients who are skeletally immature, and patients with conditions that would compromise the implant stability or the post operative recovery period.

Review of clinical data also indicates that very clearly patients with inadequate bone stock, such as severe osteopenia, patients with avascular necrosis, greater than 50 percent involvement of the femoral head, and patients with cysts, multiple cysts in the femoral head greater than one centimeter. These types of conditions are not appropriate for use of the BHR system.

Additionally, out of an abundance of caution, given the metal-metal nature of the device, we believe that women of child bearing age and patients with renal failure should be contraindicated.

Just briefly, I'll touch on training. It's our intention to send a group of what we call core surgeons to view live surgery in Birmingham, U.K., as well as receive additional lecture and workshop interactions. These surgeons would then be

the ones who would come back to the U.S. and ultimately after approval train other surgeons who have an interest in the BHR system.

This training would be held in North America, and there would also be additional information available for surgeon resources, such as surgical techniques and web site information with advice and technique information.

FDA requested us to provide a post approval study protocol, and although we do not believe necessarily that a post approval study is needed due to the long-term follow-up and large patient population we already have, we certainly submitted a protocol that was based upon a template of a previously approved device, Class III hip device that we had provided the FDA earlier. So that's the template for this, generally a prospective, nonrandomized survivorship study with clinical radiographic evaluations through five years.

Next slide.

In years six through ten, we will do postcard follow-up. Any explants returned to the

sponsor would be analyzed as appropriate, and we would make appropriate progress reports to FDA obviously.

So to round out the theme we've been building on, the device design of BHR is based upon lessons learned from previous resurfacing designs and metal-metal bearings. Extensive preclinical testing confirms the device should perform as intended in vivo. The clinical data confirms there's a reasonable assurance that the safety and effectiveness of the device.

The statistical analysis demonstrates robustness of the efficacy results, and we believe, finally, that the clinical results support the proposed labeling.

I would like to thank the panel and FDA for all of their efforts on behalf of this PMA.

Thank you.

PANEL CHAIRPERSON NAIDU: Thank you.

I'd like to thank the sponsor and the representatives for their presentations.

I'd like to address the panel now. Remember that you'll have time for questions this

afternoon, but nevertheless, if you have extensive questions for the sponsor at this point, please ask it so that they'll have some time to prepare for the afternoon session.

Does anybody on the panel have any questions at this time for the sponsor? Dr. Mabrey.

DR. MABREY: With regards to the surgical training of the core surgeons and then the subsequent training of surgeons within the United States, if you could provide us some information on the length of that training, the number of cases that they would see, whether or not observation of the trained surgeons within the United States would be performed, and how they would be evaluated as to their proficiency in implanting the device; whether or not that would be a requirement for using the device or simple attendance at the training course.

PANEL CHAIRPERSON NAIDU: Thank you, Dr. Mabrey.

Anybody from sponsor willing to tackle that question?

MR. VELEZ-DURAN: I just wanted to make

sure. So you want us to address now or later, but we're ready to address it now.

PANEL CHAIRPERSON NAIDU: Yeah, we have a little time. So we can go ahead and we've got 15 minutes before we break.

MR. VELEZ-DURAN: To discuss the issues of training we have brought a couple of people that are working very closely on the plan, and I would defer that question to one of my colleagues, and also we have some clinicians that have also participated in that discussion.

So Marc.

DR. THOMAS: My name is Dr. Marc Thomas, and I'm an employee with Smith & Nephew.

The training of the core group of surgeons will initially be a two-day, on-the-ground course associated with didactic issue and hands-on component which will be in the form of sawbones and also viewing live surgery.

After that course that they will attend, we had to time it within an acceptable period of when the people or the surgeons will get the device in

their hands. Before that occurs, we will have another meeting where, once again, there will be follow-up lectures to solidify the information for that core group of surgeons.

There will be another opportunity for a hands on component, and there will be another opportunity to view our surgery to see any tips or tricks and have an opportunity for a last question and answer session with one of the designing surgeons from the U.K.

At that stage if the FDA allows, they will be allowed access to the device and work on their own proficiency through performing the surgery on their own patients for a period of time until they feel that they have the self-proficiency to stand up and teach their colleagues.

DR. MABREY: Will there be an opportunity for cadaveric dissection as well or will the entire procedure be conducted on sawbones?

And just for the audience's clarification, sawbones are basically plastic representations of the bones without soft tissue attachments versus

cadaveric, which includes all of the soft tissue and muscle attachments.

DR. THOMAS: There will be an overture in the United States for use of the instrumentation on cadaveric specimens.

DR. MABREY: Thank you.

MR. VELEZ-DURAN: I would also like to take the opportunity to introduce Dr. Rogerson. He is a U.S. clinician from Wisconsin, and he has reviewed also our plan for training and we'd like his comments on that.

DR. ROGERSON: Thank you.

I'd like to preface this that I am an orthopedic surgeon in Madison, Wisconsin, specializing in the treatment of shoulder, hip, and knee from arthroscopy to joint replacement. I've been very active in the Arthroscopy Association, presently on the board of directors, and vice chair of the Orthopedic Learning Center where we do cadaveric courses and training for arthroscopic surgeons learning shoulder, ship, and knee arthroscopy.

I have no financial interest in this

whatsoever, although my air fare and hotel room are being reimbursed by Smith & Nephew, and my main interest in this proceeding is in trying to help facilitate the introduction of this technology in the United States. Some of that is a selfish, personal reason. I have some arthritis brewing in my hip, and I have been very interested in looking at alternative to conventional total hip arthroplasty, as a lot of my patients. And I have personally send about 30 patients over to Europe to have Dr. Kunda Schmidt perform the Birmingham replacement, and I have been basically amazed at the results of these patients coming back and their activity level.

I've also visited Dr. Schmalzeried, Michael Mont and staff here in the United States. So I have no particular allegiance to Smith & Nephew, but I do feel that the technology that is being presented to you is extremely important, and I hope that it at some point will make its way through the FDA.

In terms of the training program, which I think is imperative because when you look at this replacement; it is a different animal than a

conventional total hip replacement. You actually do not have the exposure that you'd have by cutting off the head and neck to evaluate the acetabulum.

The soft tissue dissection is critical and the learning curve for this procedure is going to be much greater for surgeons in any setting for this procedure.

Smith & Nephew, as you've seen, has had extensive experience with this procedure worldwide. They've developed a well structured, educational experience that has previously been employed in other countries, and what it really consists of is graduated release of this prosthesis into the market so that it basically guards against a full release, a full launch with poor training and ultimately poor results.

The core group of surgeons that would go to Birmingham for the two-day intensive training would be subjected to educational didactic lectures, which would go through the history of the development, the tribology, the metallurgy, the surgical technique, the indications and contraindications for the procedure, and particularly the surgical technique, and that

would be augmented by surgical observation of Dr. McMinn or Dr. Treacy, and also work with sawbones in Europe would have a hands-on laboratory in that setting.

That would hopefully be about two months before the introduction of the device on the market, and then right before the introduction of the device on the market, there would be another intensive training session for that core group of surgeons, and they would go to a learning facility, again have didactic lectures, but more importantly, more exposure to the surgical procedure both in terms of DVD/CD education. Sometimes you can actually see more. My experience at the learning center is that although the cadaveric dissection is critical, sometimes a well developed and particularly well executed DVD of the procedure where you can zoom in and show the critical parts of that procedure are equally as valuable as the cadaveric dissection.

So during that, right before the release those surgeons would be, again, educated as to the indications, contraindications, but more importantly

have a very fresh experience in terms of the operative exposure and operative technique.

They would then go back to their local setting and start performing these operations on patients. The desire of the company is to have field representatives who are very experienced in this technique, go out to this core group of physicians and observe and help in the first ten cases and to make sure that they are getting through their learning curve, and when that learning curve has -- and that may vary depending on the core group of surgeons -- but when that learning curve has been attained, then those core group of surgeons would become the teachers of the next group that would occur at the full launch.

So that when it comes time for the full launch for the rest of the United States, there would be a number of regional facilities where you have this core group of surgeons that have excellent experience. The participants would then go to a lab setting in the United States where they would go through a very similar procedure that the core group of doctors went through in England, do that in the United States and

then have the ability to have monitoring come into their OR with the field representatives, but also have the opportunity to visit the core group of surgeons, observe surgery and get the same type of course that the core surgeons got in Europe.

So I think that from my standpoint in terms of learning how to do a procedure that Smith & Nephew has thought this out. There seems to be a well structured program that has, I think, been effective worldwide up to this point, and I think that it will be even more defined and meticulous in the United States because of the wider launch that will occur here.

DR. MABREY: How many surgeries do you anticipate being part of this initial learning curve for your 15 core surgeons?

DR. ROGERSON: I think that the level of expertise in terms of comfort level in the learning curve, I would think that you would need to have probably 30 surgeries under your belt before you would start to get through the learning curve.

That could vary depending on the surgeon

and what his experience has been. For example, I've up to this point been doing a reasonable number of metal on metal, big femoral head stem prostheses. So I've got very good experience with the acetabular components of a joint replacement when it's a metal on metal.

So the learning curve of the acetabular might be easier for one surgeon versus another, but I think that it would be hard to put a number of cases on it, but I think the comfort level would be documented by the company and by the field representatives when somebody has gotten through their learning curve.

PANEL CHAIRPERSON NAIDU: Thank you. Dr. Blumenstein.

DR. BLUMENSTEIN: How many deaths were in these cohorts?

MR. VELEZ-DURAN: I'm sorry. Could you repeat the question?

DR. BLUMENSTEIN: How many patients died?

MR. VELEZ-DURAN: If you'll just wait a minute, we have the data. We're looking for it.